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(54) Title: NUTRITIONAL COMPOSITION CONTAINING METHIONINE			
(57) Abstract An enteral food composition for clinical or dietary use, comprises, in addition to carbohydrates and proteins or their hydrolysates the following components or their nutritional equivalents, per daily dosage: methionine (0.6–7 g), cysteine (0.5–2.5 g), folic acid (0.4–8 mg), pyridoxal (vitamin B ₆) (3–20 mg), zinc (18–120 mg) and at least 400 kcal energy in the form of carbohydrates. These amounts are well above the Recommended Daily Allowance (RDA) values. Further preferred components include lecithin, cyanocobalamine, betaine and magnesium, as well as transsulfuration metabolites, ATP enhancers and antioxidants.			

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Nutritional composition containing methionine

Field of the invention

The present invention relates to a module of nutritional components which supports total methionine metabolism in man, for use in a universal medicinal food. The invention also relates to food products containing this module and to a method of producing food products by using selected amounts of the module.

Background

Methionine is metabolised in man via a multi-step pathway, the transsulfuration pathway. Several intermediate products are formed in this pathway, which play a dominant role in other biochemical pathways as well. For example, the reaction product S-adenosyl methionine is extensively used in many methylation reactions; homocysteine is the main methyl acceptor in folate metabolism and also the conversion of betaine to dimethylglycine (via methylation of homocysteine) strongly influences folate metabolism.

Another intermediate in the transsulfuration pathway is cystathionine generated by reaction between homocysteine and serine, that may split into cysteine and 2-oxy-butyrate. The latter is involved in the metabolism of several other compounds (e.g. threonine). Cysteine is metabolised to various useful products such as taurine and sulphates. It is also an important precursor for glutathione in the liver and some other tissues. Glutathione that is produced in the liver has to be transported to cell compartments in some peripheral organs in order to exhibit its activity. Intracellular glutathione levels are in turn strongly influenced by the presence of reducing equivalents and amino acids in the cell.

Herein we define *total* methionine metabolism as those biochemical pathways which occur in mammals and in which metabolites of the methionine transsulfuration pathway (methionine, S-adenosyl methionine, S-adenosyl homocysteine, homocysteine, cystathionine and cysteine) and main metabolites thereof (taurine and glutathione) are involved (see scheme below).

Many diseases in man have been associated with impaired functioning of parts of total methionine metabolism. Lack of the body capacity for methylation (by shortages of available S-adenosyl methionine) has been related to diseases like cancer, improper wound healing, diabetes, neurological diseases like Alzheimer or Parkinson' disease (WO 96/33703). Shortages of folate have been associated with neural defects and several other

problems.

Dysfunction of methionine metabolism may also lead to increased homocysteine plasma levels, which are associated with cardiovascular problems. Cysteine deficiencies may lead to low taurine levels, low sulphation capacity and low intracellular glutathione levels. Shortages of cysteine have been associated with diseases like diabetes, cardiovascular disease, cancer, rheumatoid arthritis, etc.

Glutathione can play many important roles in the cell. A substantial part of glutathione must be in the reduced form (having a specific redox potential) in order to allow it to be active. Deficiencies of glutathione have been associated with all kinds of radical-mediated diseases, such as chronic inflammations, rheumatoid arthritis, with the occurrence of cancer and impaired immune functions against infection.

EP-A-532369 (Bissbort) describes the pharmaceutical use of L-methionine for enhancing the methylation capacity in man, e.g. for improving the immune response, combating viral infections and increasing creatine production. Methionine may be combined with folic acid, pyridoxine (vitamin B₆), cyanocobalamine (vitamin B₁₂) and magnesium. A daily dose comprises 1.5–5 g (3 g) of L-methionine, 250–2500 mg (600 mg) of magnesium chloride, 30–120 mg (100 mg) of magnesium carbonate, 0.6–20 mg (8 mg) of folic acid, 1.5–25 mg (10 mg) of vitamin B₆ and 15–25 µg (20 µg) of vitamin B₁₂.

WO 93/15738 (Waldthaler) discloses medicaments containing thymine or its equivalents in combination with methionine, pyridoxine and/or cyanocobalamine and optionally penicillin G for the treatment of disorders in the folate metabolism.

WO 96/02252 and WO 96/33727 (Knoll) disclose the use of S-adenosyl-L-methionine for the treatment of damage caused by temporary and permanent local ischaemias, respectively.

EP-A-347864 (Strydom) discloses an anti-atherogenic agent which lowers the plasma level of free sulphydryl groups of homocysteine and cysteine and which can contain oxidising agents and folic acid, pyridoxine (vitamin B₆), cyanocobalamine (vitamin B₁₂) and choline or betaine.

Likewise, EP-A-595005 and EP-A-595006 (Vesta) teach the use, for adults and infants respectively, of specific ratios of folic acid, pyridoxine and cyanocobalamine for suppressing high homocysteine and methionine levels in plasma, which are the cause of metabolic disturbances. According to the latter document, pyridoxine should at least

partly be present in its accessible pyridoxal form. Riboflavin (vitamin B₂), ascorbic acid (vitamin C), tocopherol (vitamin E), zinc and selenium may also be present.

EP-A-705542 discloses a complete dietary composition for adolescents and especially for children of 1 to 6 years having diseases such as intestinal disorders. The composition contains 50-65 (63) energy % of carbohydrates, 20-35 (25) en.% of fats and 10-20 (12) en.% of free amino acids with a specific amino acid content.

A multivitamin preparation supporting the immune system is disclosed in GB-A-2,292,522. It contains an amino acid blend, vitamins C, E, A, D and B complex, minerals and trace elements. Important amino acids are: methionine (90 mg), valine, leucine, threonine (70 mg), phenylalanine, lysine, isoleucine and tryptophane. Levels of B complex vitamins may be: B1 (50 mg), B2 (100 mg), B6 (100 mg), pantothenic acid (300 mg), nicotinamide (50 mg), B12 (2.5 µg), folic acid (150 µg) and biotin (50 µg). The preparation does not contain carbohydrates or full proteins. No recommended dosages are given.

US 5,215,750 discloses a composition for inducing weight loss, containing glutamine as the major component, and further a broad range of vitamins and minerals, without further amino acids, proteins, carbohydrates or fats.

Despite these proposals, the diseases referred to above are still very common and therefore there exists a need for nutritional products that may support prevention and treatment of these diseases.

Many persons suffer from deficiencies in essential amino acids, such as methionine, essential fatty acids, vitamins, minerals, trace elements or other food components, as a result of bad eating habits, disorders in nutrient absorption, or increased nutrient demands. A minority of patients suffer from metabolic disorders in the trans-sulfuration pathway; some enzymes have low activity or do not function at all. Thus there is a need for a nutritional product which supports total methionine metabolism and at the same time compensates for the shortages in nutrients that may occur in patients in need of support of methionine metabolism.

Several intermediates of total methionine metabolism can be quite reactive in the human body, and the reactive forms (reduced homocysteine, cysteine, glutathione) are not easily transported over the cell membranes. It is therefore important to support the methionine metabolism in such a way that no undesired side effects occur and at the same time intracellular levels of useful intermediates are maintained, even in the diseased state.

The reactive species are also easily oxidised in aqueous solution, and it is therefore an object of the invention to provide a nutritional composition with a sufficient shelf stability. Some nutritional components that play an important part in the methionine metabolism have bad organoleptic properties. It is therefore an object of the invention to provide a nutritional product that is well acceptable to the consumer.

Many attempts have been made up to now to find solutions to these problems. All these prior attempts have concentrated on a part of the total methionine metabolism, relying on an adequate functioning of the rest of the biochemical pathways of total methionine metabolism in man to maintain homeostasis and meet physiological demands. For supporting these parts, either too low or too high amounts were suggested.

It has now been found that it is essential to provide patients with a combination of components that play a key role in the various parts of total methionine metabolism as depicted in the scheme below, and to provide them in an excess amount in the form of a (medicated) nutritional composition in order to give nutritional support to the maximum number of patients. In this context "nutritional" means at least partly satisfying the energy needs in addition to having a medicinal effect.

It has furthermore been found to be advantageous to administer other components that play a role in total methionine metabolism as well. Such other components comprise end products and intermediates for giving a more rapid response and for meeting requirements for those patients that have deficiencies in one or more key enzymes that are involved in total methionine metabolism.

The invention pertains to an enteral food composition containing at least digestible, in particular glucose or α -glucan, carbohydrates and proteins or protein hydrolysates and a combination of active components as defined in the appending claims. The amounts of the components of the food composition of the invention are related to the Recommended Daily Allowance (RDA) and other recommendations as used in standard nutrition literature. The reference values based on these RDA values for components that can be used according to the invention, together with the preferred ranges of total intake per day, are given in table 1 below. The reference are based on healthy adults having a body weight of 70 kg. For patients of different condition and different body weight, the levels should be adapted accordingly. It is to be understood that on average the energy intake per day should be about 2000 kcal.

Where reference is made to nutritional equivalents of the components, this

includes any compound which under physiological conditions yields the component in question in equimolar amounts.

Table 1

Reference values and preferred levels according to the invention

component	reference mg/day	general mg/day	preferred mg/day
methionine/cysteine*	1100	600-7,000	1,600-4,000
folic acid	0.2	0.4-8	0.6-3
pyridoxal	2.0	3.2-20	4-12
cyanocobalamine	0.0015	0.002-0.02	0.0036-0.01
magnesium	300	200-700	300-500
riboflavin	1.5	2-10	2.5-6
niacin	17 NE	25-170	35-85
thiamine	1.5	2-10	3-6
zinc	12	24-120	24-100
manganese	6	9-60	10-30
copper	2.0	3-14	4-10
selenium	0.07	0.08-0.3	0.1-0.15
ascorbic acid	65	100-900	150-300
tocopherol	10 a-TE	15-180	20-40

* as methionine, S-adenosyl methionine, S-adenosyl homocysteine, homocysteine, cystathionine, cysteine, cystine, glutathione or other equivalents (see text).

Nutritional equivalents of amino acids include di- or oligopeptides incorporating said amino acid, esters, amides and salts of the amino acids, as well as S-substituted derivatives in the case of sulphur-containing amino acids, including methionine, S-acetylmethionine, S-acetylhomocysteine, homocysteine, cystathionine, cysteine, cystine, glutathione and other dimers and trimers derived from these. The sulphur amino acids other than methionine and cysteine can be used instead as a substitute of methionine and cysteine, although the latter two are preferred. Suitable examples of a cysteine equivalent are N-acetylcysteine and bisglycylcystine. Proteins may also be used as amino acid sources, provided that the desired amino acids become readily available by digestion.

Methionine-rich proteins include e.g. casein, caseinates and casein hydrolysates. Cysteine-rich proteins include dairy whey proteins and specific proteins thereof such as lactalbumin, as well as blood proteins, egg proteins and other proteins which are rich in sulphur-containing amino acids and hydrolysates thereof. Thus the required level of sulphur-containing amino acids can be attained e.g. by combining casein with cysteine, N-acetylcysteine or a cysteine-rich peptide or by combining whey protein with methionine or a methionine-rich peptide. Preferably, proteins that are rich in essential amino acids are also present.

Nutritional equivalents of pyridoxal (vitamin B₆) include pyridoxal phosphate, pyridoxine and pyridoxamine and salts and the like. Nutritional equivalents of niacin (nicotinic acid) include niacinamide (nicotinamide) and tryptophan. The preferred equivalent of thiamine (vitamin B₁) is its hydrochloride.

Among the components given in table 1, methionine/cysteine, folic acid, pyridoxal and zinc should be present in addition to the energy content. These components, including the carbohydrate content, were found to be essential as primary support of the transsulfuration pathway. At least half of the methionine/cysteine content should consist of methionine or a methionine equivalent. A second group of important components includes magnesium, cyanocobalamine and betaine/choline. Preferably, at least one of these is also present in the food compositions of the invention. Magnesium is preferred, but at around or slightly above the reference level only. Suitable magnesium salts include magnesium hydrogen phosphate and magnesium sulphate. A third group comprises trans-sulfuration products, including creatine, carnitine, taurine and nucleotides. At least one of these is also advantageously present in the food composition. A fourth group of components is important as they stimulate carbohydrate metabolism and produce ATP and reducing equivalents. At least one member of this group which includes pyruvate, thiamine, riboflavin, niacin, biotin and thioctic acid, is preferably present as well. A final group comprises ascorbic acid, tocopherol, selenium, copper and manganese. The incorporation of ascorbic acid and/or tocopherols is preferred for ensuring that reduced glutathione is spared from excessive attack by radicals or oxidation processes. Ascorbic acid may be present as a nutritionally acceptable salt, and tocopherol as any one or a combination of isomers, e.g. tocopherol. Other antioxidants or radical scavengers like carotenoids, flavonoids, uric acid etc. may be included as well. Similarly, the trace elements Cu, Se and Mn are preferably included, as they are essential for key enzymes

that neutralise oxygen-containing radicals. The preferred range for Cu and Mn is 2–5 times the reference value; for selenium it is about 1.5 times the reference value.

The other components of table 1 are also preferred individually, i.e. the selection of a single component, e.g. riboflavin or manganese, forms a distinct embodiment of the invention. Components for which a reference level is not given in table 1, are also advantageously incorporated in the composition of the invention. The methyl donor betaine (N,N,N-trimethylglycine, as its inner salt or its hydrochloride) and/or one of its precursors choline and phosphatidylcholines (occurring in certain lecithins) is preferably included in order to stimulate an independent pathway for the conversion of homocysteine to methionine. For reasons of taste, betaine itself is preferred over its equivalents.

Creatine (N-guanidyl-N-methylglycine) can be incorporated as such, as its phosphate or as an analogue such as guanidine derivatives, in the levels indicated, with a preferred level of around 10 g/day. L-Carnitine can be given as such (inner salt) or as its hydrochloride. Creatine and/or carnitine are especially preferred for patients having a poor blood circulation, or suffering from local ischaemic conditions. D-Biotin (generally preferred) and taurine can be included as such, taurine especially for infants and neurological patients. Nucleotides can also be advantageously included, preferably as yeast extract in an amount of about 0.1–4 g/day, for example in products for the treatment of inflammatory diseases of the gut.

Pyruvate is another component that can contribute to the ATP production and can protect glutathione as a radical scavenger. The preferred level is from 2 to 20 g/day, especially 4–8 g/day. Pyruvate can be incorporated e.g. as free acid or as its Ca, Na or K salt. DL-Thioctic acid (lipoic acid) is also preferred for increasing the level of ATP produced. Niacin, riboflavin and thiamine also stimulate carbohydrate metabolism and produce ATP and reducing equivalents.

Furthermore, usual components can be incorporated at or above the recommended amounts, especially calciferol/cholecalciferol/dihydrocalciferol (vitamin D) and phosphate. The composition should comprise sufficient levels of essential amino acids such as lysine in accessible form, so that the total intake corresponds at least to the reference levels. Some non-essential amino acids are also preferably included in the composition of the invention. These comprise especially serine, and furthermore glutamine and arginine/ornithine at the indicated levels as such (L-form) or as easily degradable peptides or proteins. Threonine is preferably not present in important amounts,

i.e. preferably lower than 5.2 g per 6.25 g of nitrogen (< 5.2 g per 100 g of proteinaceous material). Proteins which are low in threonine include acid whey.

The compositions contain carbohydrates, preferably proteins and preferably fats. In a complete food, the carbohydrates should constitute at least 25% of the required energy content, i.e. at least 400 kcal/day, up to 1500 kcal/day. The carbohydrates can
5 comprise mono-, di-, oligo- and polysaccharides, such as glucose, fructose, maltose, sucrose, fructo-, galacto- and especially gluco-oligosaccharides, starch, starch hydrolysates and starch fractions and the like. The carbohydrate composition can be adapted to the type of patients. For diabetes patients, slowly degrading carbohydrates like fructose
10 polymers may be present together with a relatively large amount of high molecular weight maltodextrins. Generally, the carbohydrate compositions is low in lactose. The compositions may furthermore contain dietary fibres such a non-digestible carbohydrates. The proteins may be those described above as sources for the desired amino acids, including milk proteins, egg proteins, blood proteins. For reasons of taste, it is preferred
15 that at least half of the total proteinaceous material (proteins, hydrolysates and amino acids) is in the form of proteins or peptides, especially in the form of intact proteins.

The fats may comprise normal fats C_{12} - C_{18} derived from saturated and especially unsaturated fatty acids. The fats may include medium chain triglycerides derived from C_8 and C_{10} fatty acids (e.g. accounting for 5-40 wt.% of the fats), and
20 preferably polyunsaturated long-chain ($\geq C_{18}$) fats (PUFA's) derived from ω -3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (preferably at least 3 wt.%, in particular 5-15 wt.% of the fats). The ω -3/ ω -6 ratio is preferably from 0.3 to 3. For complete foods, the fat content is preferably more than 30 % of the total energy content, especially more than 35 en.%, up to 45 en.%. The fats should contain phospho-
25 lipids such as lecithin or an equivalent thereof at a level of 1-20 wt.% of the fat content, or 0.3-10 en.%, preferably 0.6-5 en.% of the composition. The phospholipids can be partly (i.e. the amount above 5 wt.% of the fat content) substituted by equivalents such as choline or betaine.

The food composition can have the form of a complete food, i.e. all the
30 nutritional needs of the user. As such it will usually containing 1200-2500 kcal per daily dosage, apart from higher or lower amounts in exceptional cases. The daily dosage amounts are given with respect to a daily energy supply of 2000 kcal, but can be adapted accordingly. The complete food can be liquid, wherein the daily dosage is contained in

e.g. 2000 ml; more diluted or, especially, more concentrated liquids can also be used. The composition and also be in solid form for reconstitution with water. The complete food can be in the form of multiple dosage units, e.g. from 3 to 10 per day.

The food composition of the invention can also be a food supplement to be used
5 in addition to a non-medicinal food, containing less than 1500 kcal, in particular 400–1000 kcal, per daily dosage. Such food supplement preferably also contains at least part of the carbohydrate and protein supply, so that the need of essential amino acids and serine is met with the supplement. A very useful supplement contains the essential components at the levels indicated above (methionine/cysteine, folic acid, vitamin B₆,
10 zinc and optionally magnesium, vitamin B₁₂, betaine/choline, serine and/or tryptophan with a suitable carrier such as maltodextrin in dry form, e.g. in sachets of 10 g. The content of the sachet may be added to regular food or to food components so as to provide the daily doses according to the invention.

The invention also relates to a process of producing a food composition, which
15 comprises preparing a premix of at least said methionine/cysteine, folic acid, pyridoxal and zinc, optionally with a relatively small amount of maltodextrin or other carbohydrate as a carrier. Further components are then added to said premix, for example by subsequent addition of other premixes. The use of premixes may simplify and/or standardise the preparation of especially adapted food compositions directed at specific
20 needs. Also from an economical point of view, and from the point of view of minimising mistakes during processing, it is therefore advantageous to produce a single premix of components that can be used in the manufacture of several types of enteral clinical nutrition.

As the module of components supports total methionine metabolism, it has
25 universal benefit in many types of clinical nutrition. The universal character of the food composition of the invention obviates the need to await the result of some types of clinical analyses of patients. The module can added in response to specific nutritional demands. The compositions can be adapted for clinical nutrition, infant formulae, nutrition for persons at risk for specific diseases, enteral nutrition during pregnancy, and
30 dietetic supplements. The food compositions can be used for the treatment or prophylaxis of increased plasma level of homocysteine, cardiovascular diseases, impaired immune function, inflammatory diseases, autoimmune diseases such as arthritis, wound healing after surgery, decubitus, cancer, premature ageing, allergic conditions, neural disorders,

Example 1

Three standard mixtures of active components were prepared by dry mixing the amounts as indicated in tables 2 and 3 and optionally table 4.

Table 2*Ingredient mixture A for support of total methionine metabolism*

	amount per 100 kg of premix A
maltodextrins	74 kg
L-methionine	8 kg
N-acetylcysteine	2 kg
folic acid	6 g
pyridoxine	60 g
zinc sulphate	500 g (= 200 g Zn)
cyanocobalamine on carrier	30 g (= 30 mg B12)
magnesium phosphate 3 aq.	14 kg (= 2 kg Mg)

Table 3*Ingredient mixture B for support of total methionine metabolism*

	amount per 100 kg of premix B
maltodextrins	89 kg
betaine	10 kg
nicotinamide	510 g NE
riboflavine	30 g
thiamine.HCl	30 g
manganese sulphate 4 aq.	320 g (= 80 g Mn)
cupric sulphate 5 aq.	150 g (= 40 g Cu)

Table 4*Ingredient mixture C for support of total methionine metabolism*

		amount per 200 kg of premix C
	maltodextrins	40 kg
5	creatine	100 kg
	L-carnitine	12 kg
	taurine	400 g
	ascorbic acid	2.0 kg
	alfa-tocopherol	200 g TE
10	soy lecithin	5 kg
	L-biotin on a carrier	200 g (= 2 g L-biotine)
	sodium selenate on a carrier	370 g (= 1 g Se)
	L-serine	30 kg
	L-tryptophan	10 kg

Example 2***Complete enteral tube feeding in dry form.***

The ingredients as listed below are dissolved in 2000 l water.

Composition of aqueous phase of complete enteral nutrition

		amount per 2000 l
20	caseinates (50% Na, 50% Ca)	60 kg
	protein isolate from acid whey	40 kg
	ingredient mixture A	10 kg
	ingredient mixture B	10 kg
	ingredient mixture C	20 kg
25	maltodextrins	280 kg
	L-arginine	6 kg
	wheat hydrolysate	30 kg
	fibres (inulin/soy: 2/1)	16 kg
	calcium phosphate	0.6 kg
30	magnesium phosphate	0.4 kg
	sodium chloride	0.9 kg
	potassium citrate	5 kg
	lecithin	4.4 kg
	standard trace element premix	250 g
35	(which comprises 20 g Fe, 3 g Cu, 100 mg Mo, 2 mg F, 20 g Zn, 6 g Mn, 66 mg Cr, 200 mg I, 40 mg Co and 10 g Se)	
	standard vitamin premix	20 g

(which comprises pantothenic acid 8 g, thiamine 2 g, riboflavin 2.2 g, niacin 4.2 g NE, vitamin B6 2.6 g, biotine 200 mg and folic acid 260 mg)

meso-inositol 50 g

yeast extract 1 kg

5 After dissolving the ingredients, the aqueous phase is set on pH 6.5–8 and stirred until use. In a separate tank the fat blend as exemplified below is prepared by methods known in the art (pumping the appropriate amounts in the tank at elevated temperature (e.g. 50°C) and the fat-soluble vitamins (A, D2, K and E) are added and the mixture stirred until use).

10 *Fat blend composition; amounts in kg per 100 kg*

sunflower oil (high oleic acid) 28

sunflower oil 12

rapeseed oil 52

fish oil (high DHA) 2

15 MCT oil 6

vitamin premix

vitamin A 1.4 g

vitamin D2 10 mg

vitamin K 100 mg

20 vitamin E 100 g

The aqueous phase is pumped to a homogeniser arranged before a pasteuriser and static mixer. The fat phase is carefully dosed to the aqueous phase before it reaches the mixer, in a ratio of 1 part fat phase to 16 parts of the pasteurised aqueous phase. Immediately thereafter the mixture is homogenised and pumped to a heat exchanger
25 where the water is evaporated and the resulting product spray-dried and packed in cans.

Example 3

A nutritional supplement for the elderly

In 2000 liter tap water are dissolved:

30 70 kg skimmed milk powder (delactosed)
64 kg saccharose
5 kg soy lecithin
10 kg algae oil
10 kg canola oil

This mixture is pasteurised and fermented.

Then are added:

- 20 kg mixture A (of example 1)
- 6 kg pectine
- 200 kg glucose syrup (Glucidex)
- 5 2 kg choline chloride
- 2.4 kg calcium chloride
- 2.4 kg potassium phosphate
- 1.5 kg potassium lactate
- 260 g sodium ascorbate
- 10 2.0 kg potassium citrate
- 40 kg fruit concentrate
- 1 kg flavourings

The mixture is set on pH 3.8–4.4, pasteurised and filled aseptically into 500 ml cartons.

Example 4

- 15 *Supplement for persons with volume restrictions (infants, persons suffering from illness, cancer or neuropathic diseases)*

Packed in 1 liter cartons.

		Amount per 100 ml
	Energy	150 kcal
20	Protein (casein/whey 80/20)	8.2 g (= 0.3 g Met + Cys)
	Tryptophan	0.1 g
	Carbohydrates	16.5 g
	Maltodextrin	10.5 g
	Sucrose	6.0 g
25	Fats	5.5 g
	Saturated	1.3 g
	Mono-unsaturated	1.8 g
	PUFA's	2.1 g
	from vegetable oils, lecithin + DHA/EPA source (0.1 g)	
30	Fibre (inulin/soy 1:1)	0.4 g
	Sodium	60–100 mg
	Potassium	140–210 mg
	Chloride	80–150 mg
	Calcium	230 mg
35	Phosphorus	150 mg
	Magnesium	35 mg
	Iron	2.0 mg

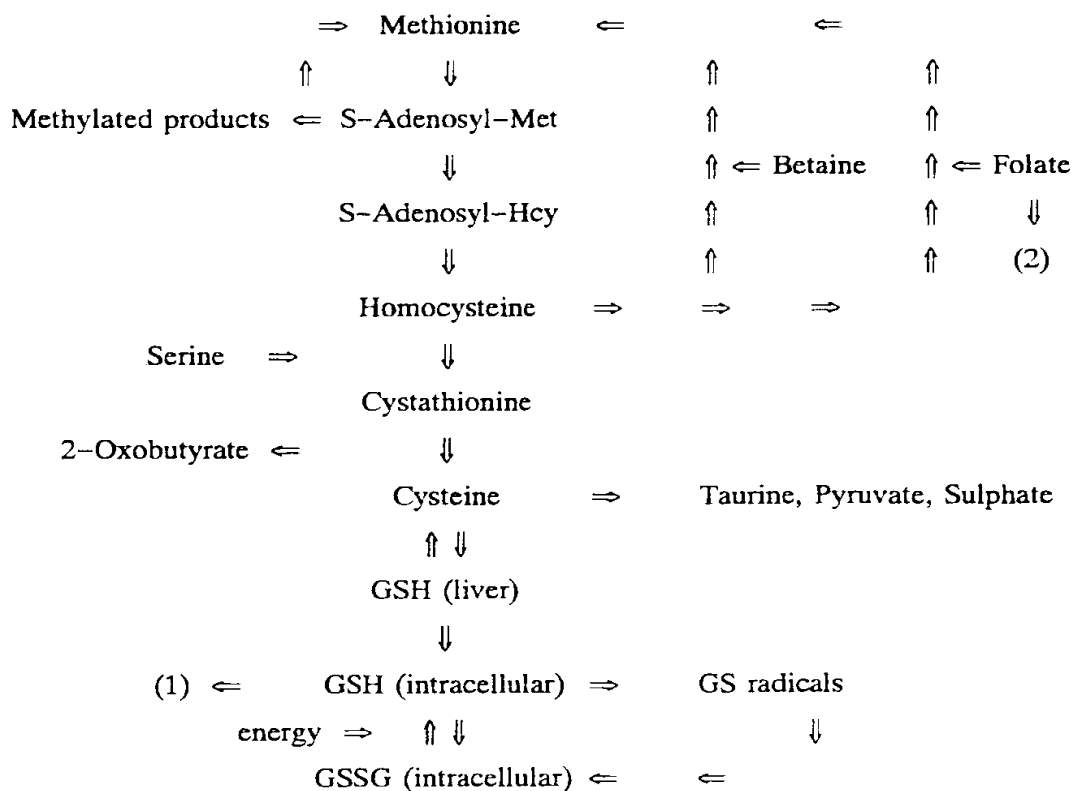
	Zinc	6.0 mg
	Copper	0.6 mg
	Manganese	2.0 mg
	Fluorine	0.2 mg
5	Molybdene	10 µg
	Selenium	10 µg
	Chromium	6.6 µg
	Iodine	20 µg
	Vitamin A	166 µg RE
10	Vitamin D	2.0 µg
	α-Tocopherol	4.9 mg
	Vitamin K	8.0 µg
	Thiamine	0.4 mg
	Riboflavin	0.4 mg
15	Niacin	6 mg NE
	Pantothenic acid	0.8 mg
	Vitamin B ₆	1.0 mg
	Folic acid	100 µg
	Vitamin B ₁₂	0.3 µg
20	Biotin	20 µg
	Vitamin C	13 mg
	Betaine	20 mg
	Taurine	4 mg

Example 525 ***Food supplement***

The mixture of table 2 (example 1) was filled in sachets of 10 g each.

Scheme of methionine metabolism

(Met = methionine, Hcy = homocysteine, GSH = reduced glutathione, GSSG = oxidised glutathione)



(1) Cofactor function, Amino acid Transport and Detoxification

(2) Pyrimidine metabolism, One-carbon Pool and Gly/Ser metabolism

Claims

1. Enteral food composition for clinical or dietary use, comprising per daily dosage: at least 400 kcal of carbohydrates, at least 20 g of proteins, protein hydrolysates and/or amino acids, at least 50% thereof being present as proteins, as well as the following components or their nutritional equivalents: methionine and cysteine at least 0.6 g, folic acid at least 400 µg, pyridoxal (vitamin B₆) at least 3.2 mg, and zinc at least 24 mg.
2. Food composition according to claim 1, wherein at least one of said components is comprised in the following amounts, per daily dosage: methionine and cysteine (1.6–4 g), methionine accounting for at least half of said amount, folic acid (0.6–3 mg), pyridoxal (4–12 mg), zinc (30–100 mg), and at least 800 kcal in the form of carbohydrates.
3. Food composition according to claim 1 or 2, further containing at least 0.8 g, preferably 1.6–12 g of phospholipids, per daily dosage.
4. Food composition according to any one of claims 1–3, further comprising at least one of the following components or their nutritional equivalents, per daily dosage:
 - (a) cyanocobalamine (vitamin B₁₂) (2–20 µg, preferably 3.6–10 µg), magnesium (200–700 mg, preferably 300–500 mg) and betaine and/or choline (0.3–6, preferably 0.6–3 g);
 - (b) creatine (0.5–40, preferably 2–25 g), carnitine (0.2–4, preferably 0.4–2 g), taurine (15–150, preferably 30–80 mg), and nucleotides (0.1–4, preferably 0.4–2 g);
 - (c) pyruvate (2–20, preferably 4–8 g), riboflavin (vitamin B₂) (2–10 mg, preferably 2.5–6 mg), niacin (25–170 mg, preferably 35–85 mg), thiamine (2–10 mg, preferably 3–6 mg), D-biotin (50–500, preferably 100–300 µg), and thiocctic acid (5–200, preferably 10–50 mg);
 - (d) manganese (9–60 mg, preferably 10–30 mg), copper (3–14 mg, preferably 4–10 mg), selenium (80–300 µg, preferably 100–150 µg), ascorbic acid (vitamin C) (100–900 mg, preferably 150–300 mg), and tocopherol (vitamin E) (15–180 mg, preferably 20–40 mg);
 - (e) serine (3–12 g) and optionally arginine or ornithine (2–10 g), glutamine (5–30 g), the composition being low in threonine;and preferably at least one component from each of the groups (a–c).

5. Food composition according to any one of claims 1-4, which is in a liquid form having an energy density of at least 1, up to 2.5, kcal/ml.
6. Food composition according to any one of claims 1-4, which is in a powder form to be reconstituted with water.
7. Food composition according to any one of claims 1-6, which is a complete food, containing 1200-2500 kcal per daily dosage, at least 30 energy% of which is in the form of lipids, further containing at least 70 g per daily dosage of proteins, protein hydrolysates and amino acids, at least 50% thereof being in the form of proteins, and at least 1 g of methionine and at least 0.5 g of cysteine per daily dosage, the composition optionally being in the form of multiple dosage units.
8. Food composition according to any one of claims 1-6, which is a food supplement to be used in addition to a non-medicinal food, containing less than 1500 kcal, in particular 400-1000 kcal, per daily dosage, at least 100 g of which is in the form of soluble digestible carbohydrate, and optionally further nutritional components.
9. Process of producing a food composition according to any one of claims 1-9, which comprises preparing a premix of at least said methionine/cysteine, folic acid, pyridoxal and zinc, optionally with carbohydrate as a carrier, and adding further components to said premix.
10. Use of a food composition according to any one of claims 1-9 for the treatment or prophylaxis of increased plasma level of homocysteine, cardiovascular diseases, impaired immune function, inflammatory diseases, autoimmune diseases, arthritis, wound healing after surgery, decubitus, cancer, premature ageing, allergic conditions or neural disorders.

INTERNATIONAL SEARCH REPORT

Internat. Application No
PCT/NL 98/00408

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A23L1/305 A61K31/195 A23L1/302 A23L1/304 A61K33/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A23L A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GB 2 292 522 A (GITTA CARMEN CONWAY) 28 February 1996 cited in the application see claims 1,5,6,8-13,19 ---	1-10
Y	US 5 215 750 A (KEANE MICHAEL A.) 1 June 1993 cited in the application see claims 1-7; example 2 ---	1-10
A	EP 0 259 167 A (MILLMAN, PHILLIP LOWELL) 9 March 1988 ---	1,4
A	EP 0 482 715 A (LUCA, MAURIZIO C/O INTERNATIONAL HUMAN NUTRITION) 29 April 1992 see page 6, line 17; claims 1,2,4-14 --- -/-	1-10

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

1 October 1998

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/NL 98/00408

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 532 369 A (BISSBORT, SIEGBERT H.) 17 March 1993 cited in the application -----	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No

PCT/NL 98/00408

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2292522 A	28-02-1996	NONE	
US 5215750 A	01-06-1993	NONE	
EP 259167 A	09-03-1988	US 4871550 A	03-10-1989
EP 482715 A	29-04-1992	US 5132113 A	21-07-1992
		AT 142435 T	15-09-1996
		CA 2054268 A	27-04-1992
		DE 69122025 D	17-10-1996
		DE 69122025 T	23-10-1997
		DK 482715 T	03-03-1997
		ES 2094788 T	01-02-1997
		GR 3021978 T	31-03-1997
		JP 4346770 A	02-12-1992
		US 5242697 A	07-09-1993
EP 532369 A	17-03-1993	AP 387 A	31-07-1995
		AU 666490 B	15-02-1996
		AU 2352792 A	18-03-1993
		CA 2078019 A	14-03-1993
		US 5545670 A	13-08-1996